Molecular profiling of premalignant lesions in lung squamous cell carcinomas identifies mechanisms involved in stepwise carcinogenesis.

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Public Summary:
It is thought that squamous lung cancer arises in a stepwise fashion from normal stem cells to premalignant lesions to invasive lung cancer. This study used a special technique to isolate stem cells and cells of premalignant lesions from the airways of patients with squamous lung cancer. It was also used to remove tumor cells from the same patient tissues. Studies of the gene expression profiles of these sets of samples from individual patients were analyzed to determine which pathways were turned on or off in stem cells of the airway as compared to premalignant lesions and squamous lung cancer. Some of the interesting pathways found involve cell metabolism which was found to be altered in the cells of the premalignant lesions and further altered in the tumor cells. Some pathways associated with oncogenes were predicted to be activated in the premalignant lesions although the gene expression levels were not different and similarly tumor suppressor gene pathways were predicted to be down regulated in the cells of premalignant lesions. This study begins to shed some light on the stepwise progression of squamous lung cancer and provides the first resource of gene expression data for the research community.

Scientific Abstract:
Lung squamous cell carcinoma (SCC) is thought to arise from premalignant lesions in the airway epithelium; therefore, studying these lesions is critical for understanding lung carcinogenesis. Previous microarray and sequencing studies designed to discover early biomarkers and therapeutic targets for lung SCC had limited success identifying key driver events in lung carcinogenesis, mostly due to the cellular heterogeneity of patient samples examined and the interindividual variability associated with difficult to obtain airway premalignant lesions and appropriate normal control samples within the same patient. We performed RNA sequencing on laser-microdissected representative cell populations along the SCC pathologic continuum of patient-matched normal basal cells, premalignant lesions, and tumor cells. We discovered transcriptomic changes and identified genomic pathways altered with initiation and progression of SCC within individual patients. We used immunofluorescent staining to confirm gene expression changes in premalignant lesions and tumor cells, including increased expression of SLC2A1, CEACAM5, and PTBP3 at the protein level and increased activation of MYC via nuclear translocation. Cytoband enrichment analysis revealed coordinated loss and gain of expression in chromosome 3p and 3q regions, respectively, during carcinogenesis. This is the first gene expression profiling study of airway premalignant lesions with patient-matched SCC tumor samples. Our results provide much needed information about the biology of premalignant lesions and the molecular changes that occur during stepwise carcinogenesis of SCC, and it highlights a novel approach for identifying some of the earliest molecular changes associated with initiation and progression of lung carcinogenesis within individual patients.

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